REMARKS

I. Support for the Amendments

The term "comprising" was deleted from the independent claims because it is unnecessary for defining the invention, and it was the subject of disagreed meaning between the Applicants and the Examiner. The amendment is not intended to narrow the claims, because the claims already contained a size limitation as to the number of amino acids, and because the claims still permit addition of other substances, such as labels, therapeutic agents, cytotoxic moieties, and other substituents, many of which are described in the application. (See, e.g., pp. 18, 24, 32, and 34.) The purpose of the amendment is to expedite prosecution and not to narrow the scope of the claims.

The amendment to claim 4 added limitations found in canceled claims 5-11.

The amendment to claim 27 to recite "a label" and for new claim 75 finds support at page 18, lines 5-9.

With any amendments filed in this application, the Applicants reserve the right to pursue original claims and originally claimed subject matter in subsequent prosecution, and/or in divisional or continuing applications.

II. The Rejection Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn.

The Examiner maintains the rejection of claim 12 based on the recitation of "Y_1" or "Y_2" in the peptide sequence. The Examiner rejected claims 21 and 22 alleging that the terms "X_1", "X_2", "X_3" and "X_4" are indefinite, because it is not clear "which particular" amino acids are within the scope of the claim.

Each claim at issue explicitly states that positions Y_1 and Y_2, or X_1, X_2, X_3 and X_4 are specifically contemplated to be amino acids. The Examiner contends that the specification only discloses that particular amino acids may be in these positions, and implies that the claims should be limited as such. The Examiner unnecessarily places restrictions in the claimed peptides that are not in the claims or the specification. The X_1, X_2, X_3 amino acids specifically identified by the Examiner (LTI) are simply amino acids exemplified at these positions in the specification, and are not limiting. The claims are not written in "means plus function" language, and

accordingly, it is improper to construe the claims under §112, sixth paragraph, to be limited to amino acids exemplified in the application. The specification clearly discloses that the residues may be any amino acids (page 16, lines 3-7, and page 17, lines 11-16). The specification clearly sets out what any amino acid is, and as such, a worker of ordinary skill in the art would have no difficulty determining the metes and bounds of the claimed peptides. Further, claims 12, 21 and 22 depend from claim 1, and amendment of claim 1 to remove the "comprising" language obviates the Examiner's further rejection of the claims on this basis.

Because the claims clearly define the subject matter of the invention, the rejection of claims 12, 21 and 22 under 35 USC §112, second paragraph, should be withdrawn.

III. The Rejection Under U.S.C. §102(b) Should Be Withdrawn

The Examiner maintains a rejection of claims 21-22 under 35 U.S.C. § 102(b) as allegedly anticipated by Hirohashi. Hirohashi discloses a 1502 amino acid rat protein (MLP-1) which includes within this long sequence a (partial) amino acid sequence (GYWLSLWA). Based on this partial sequence, which the Examiner identified as GYWISWA, the Examiner asserts that Hirohashi's protein anticipates claim 21 ($GYWX_1X_2X_3W$), or claim 22 ($GYWX_1X_2X_3WX_4$). Applicants respectfully traverse.

Hirohashi's 1502 amino acid protein has never been shown or suggested to bind VEGFR-3 as required by the claims, and there is no basis to assume that it would. Thus, the reference fails to satisfy a functional limitation of the claims. This difference alone is sufficient to overcome a rejection based on anticipation.

The claims also specify a peptide whose amino acid sequence is no larger than about 100 amino acids, and Hirohashi's polypeptide is much larger. In fact, claim 21 was amended herein to remove the term "comprising," which appears to have been a stumbling block with the Examiner in terms of claim interpretation. Thus, the 1502 amino acid protein taught in the reference clearly fails to satisfy the size (structural) limitations of the claims. Hirohashi does not teach or suggest peptide fragments of 100 amino acids of the 1502 residue protein that include the specified sequence identified by the Examiner through hindsight.

Thus, the cited reference fails to satisfy both structural and functional limitations of the claims, and the rejection of claims 21-22 under 35 U.S.C. § 102(b)should be withdrawn.

IV. The Rejection of Claims 21-23 Under 35 U.S.C. §103(a) Should Be Withdrawn.

The Examiner asserted that claims 21-23 are allegedly unpatentable under 35 U.S.C. 103(a) over Hirohashi, further in view of U.S. Patent No. 6,121,416. As stated previously, Hirohashi discloses a large protein of 1502 amino acids that is wholly unrelated to the VEGF family of proteins. A worker of ordinary skill would not look to Hirohashi to find a peptide that binds to VEGFR-3. Hirohashi only discloses a large protein, and makes no suggestion that a worker of skill should cleave the protein to smaller peptides of 100 amino acids or less and then attempt to select a peptide that binds to VEGFR-3. While the '416 patent teaches that peptides can be stabilized by adding cysteine residues to the ends, it does not provide any suggestion or motivation to take the large protein disclosed in Hirohashi, cleave the protein to smaller peptides, and add cysteine residues to obtain the claimed VEGFR-3-binding peptides of claims 21-23. A worker of ordinary skill in the art, reading either Hirohashi or the '416 patent, has no motivation to combine the references to obtain the claimed peptide compositions. Moreover, even if the references were combined they would not result in the production of peptides of the invention in the absence of improper hindsight.

Because there is no motivation to combine the references, nor suggestion to arrive at the claimed invention even after the references are combined, and no reasonable expectation of success for a person of ordinary skill in the art, the rejection of claims 21-23 under 35 U.S.C. § 103(a) should be withdrawn.

V. The Rejection Under 35 U.S.C. §112, First Paragraph - Enablement, Should Be Withdrawn

The Examiner maintains a rejection of claims 1-13 and 21-28 under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the description of the specification. The Examiner contends that Applicants have not taught how to make all isolated peptides comprising the claimed peptides (X_1-X_8, $GYWX_1X_2X_3W$, etc.) of 8-100 amino acids in length, and contends

that there is insufficient guidance as to which larger peptides "comprising" the smaller peptide would maintain structure and function of binding to VEGFR-3. Applicants respectfully disagree.

The claims are directed to a peptides of 8-100 amino acids, wherein the peptide includes a particular sequence of amino acids recited in the claims. Applicants have fully enabled a worker of ordinary skill in the art to make and use a peptide of 8-100 amino acids comprising the claimed shorter peptides. For example, the specification at page 35, line 8, to page 38, line 6, teaches methods for making peptides of varying lengths using techniques common in the art such as solid phase synthesis, preparation from a phage library, and recombinant expression systems. The specification indicates that a worker of ordinary skill can prepare a phage display library having peptides of a desired length range, e.g., from 4 to about 80 amino acids (Koivunen et al., *J Nucl. Med.* 40:883-88, 1999; Heiskanen et al., *Virology* 262:321-32, 1999, abstracts included), and also teaches that the peptide may be a part of a fusion protein or a chimeric protein, e.g. a GST fusion protein (see page 38). It is irrelevant that the claims do not recite a fusion protein such as GST as the Examiner contends, a worker of ordinary skill would understand from the disclosure in the specification that fusion proteins of any type are contemplated and guidance is provided in the specification for making such fusion proteins. This clearly teaches that a peptide of 8-100 amino acids in length is not out of reach of the ordinary worker.

In addition to the teachings in the specification, a worker of ordinary skill in the art would readily understand how to make a peptide comprising a specific 8 amino acid sequence within a larger sequence of 8-100 amino acids based on common knowledge in the art. For example, it is well-within the skill of the ordinary worker to use a peptide synthesizer or recombinant DNA techniques to make a string of amino acids in a specific sequence, or to have a specific sequence within a random assortment of peptides. Alternatively, it is well-within the skill of the ordinary worker to include a specific 8 amino acid sequence to the end of, or within the middle of, a known protein. The Examiner has failed to explain why well-known synthetic and recombinant techniques are not suitable for making substantially every polypeptide within the scope of the claims.

Further, the specification provides guidance as to which peptides of the invention would exhibit binding to VEGFR-3. Methods for assaying binding to VEGFR-3 are set forth in

the specification (page 42, line 1, to page 53, line 2), and it is well within the skill of the ordinary worker to generate peptides having amino acid substitutions of the peptide sequence and, without undue experimentation, determine if the substituted peptides bind VEGFR-3. The assays used to determine binding to VEGFR-3 are adaptable to a type of high-throughput assay and would produce rapid results. Moreover, the specification provides numerous working examples of peptides isolated from a phage display library that bind VEGFR-3 (see Table 1). Despite the fact that the working examples describe peptides of 10 amino acids or less, there is no reason to expect that screening the binding of larger peptides would be more burdensome to the worker of skill as suggested by the Examiner. The assay described herein is used to screen whole proteins (e.g., VEGF-C and VEGF-D) of significantly longer sequence than the peptides contemplated by the invention. The assay is not dependent on the size of the peptide and the working examples in the specification exemplify the assay, not limit it.

With respect to claim 12, the examiner asserted in the Final Action that Applicant has only enabled the peptide having "Y_1" or "Y_2" when the amino acids are cysteines. The claim at issue explicitly states that positions Y_1 and Y_2 are contemplated to be amino acids. Applicants submit that the specification clearly discloses that the residues may be any amino acids (page 16, lines 3-7, and page 17, lines 11-16), and sets out exemplary peptides of the invention wherein the "Y_1" or "Y_2" residues are cysteines. As explained above, both synthetic and recombinant techniques permit the making of claim 12 peptides where Y_1 and Y_2 are any amino acid without undue experimentation. These peptides are then assayed using methods described in the specification for their binding to VEGFR-3. Thus, the specification is enabling for a worker of ordinary skill in the art to make a peptide having the amino acid sequence in claim 12, wherein the amino acid at position "Y_1" or "Y_2" is <u>any</u> amino acid, and the peptide binds VEGFR-3.

With respect to claims 21 and 22, the Examiner asserted in the Final Action that the specification does not provide guidance for an amino acid having the sequence GWY $X_1X_2X_3W$ or GWY $X_1X_2X_3WX_4$. The specification sets out at page 17, lines 11-16, that X_1, X_2, X_3 and X_4 can be any amino acid, and the specification discloses how to make (synthetically or recombinantly) a peptide having any amino acids at these positions. Moreover, the number of 7-mer or 8-mer embodiments encompassed by the claims is finite and screening for VEGFR-3 binding activity is routine. In this respect, the claims are much narrower than "percent identity"

sequence claims that the PTO routinely allows in biotechnology patents[1]. Thus, there is sufficient guidance to make and use the invention of claims 21 or 22.

With respect to claim 30, the Examiner asserted in the Final Action that the specification does not provide guidance for a peptide of the invention and a "therapeutic protein amino acid sequence." Page 18, line 26, to page 19, line 7, of the specification describes that the peptide sequence can be attached to any second therapeutic agent, including cytotoxic agent or a therapeutic protein, such as TNF, wherein that protein therapeutic is a chimeric protein comprising a therapeutic protein amino acid sequence attached to a peptide of the invention. A worker of skill would readily understand that a therapeutic protein is any protein that has advantages as a therapeutic agent in various diseases, including cancers. A worker of ordinary skill would also understand that a therapeutic protein amino acid sequence was the underlying sequence of any therapeutic protein, such as TNF, and others known in the art, such as interleukin 2 (Davis et al., *Cancer Immunol Immunother.* 52:297-308, 2003), and interleukin-6 (Kreitman et al., *Blood* 79:1775-80, 1992)(abstracts submitted in response of 10/20/04), which may be attached to a peptide of the invention using recombinant DNA techniques. Page 38 of the specification teaches methods for making chimeric and fusion proteins comprising the peptide of the invention by recombinant techniques. Because the starting peptide is enabled as described above, and a therapeutic protein is enabled by the specification, the specification allows a person of ordinary skill to make and use the invention of claim 30.

With respect to claim 31, directed to a peptide of the invention comprising TNF, the Examiner asserted in the Final Action that because claims 1 and 21 are not enabled, claims dependent from those are not enabled. Applicants submit that claims 1 and 21 are enabled for the reasons set out above, and therefore claims dependent from those are enabled.

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[1] Example 14 of the US PTO Written Description Guidelines Training Materials (reproduced as Exhibit 1 in Applicant's response of October 20, 2004) describes a claim to a hypothetical genus of proteins claimed with the transition "having" and embracing a specific amino acid sequence and "variants" having a defined sequence similarity (at least 95%). In its analysis, the Patent Office explicitly observed that "the protein claimed may be larger than SEQ ID NO: 3" because the transition "'having' is open language, equivalent to 'comprising'," and concluded that the genus claim was adequately described, stating that "one of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus."

With respect to claims 32 and 34-37, the Examiner asserted in the Final Action that because claims 1 and 21 are not enabled, the specification does not provide guidance for the binding specificity of all antibodies or fragments thereof comprising the peptides. The specification, at page 19, lines 8-11, sets out the types of antibodies contemplated by the invention. A person of ordinary skill recognizes that any of the antibodies specified could be linked to a peptide of the invention, using well-known techniques in the art. Thus, because claims 1 and 21 are enabled for the reasons set out above and the specification describes antibodies contemplated by the invention, claim 32 and 34-37 are enabled.

With respect to claim 33 and claims 34-37, the Examiner asserted in the Final Action that the specification does not provide guidance for a "modification" that would increase the half-life of the peptide *in vivo*. Page 19, lines 12-18, describes that standard pharmaceutical and formulation chemistry techniques are used to achieve increased peptide half-life, including glycosylation, pegylation, inducing non-hydrolyzable bonds, mixing with pharmaceutically acceptable carriers and adjuvants, and the like. The Examiner's requirement that only one of these should be used as a modification increasing serum half-life is unnecessarily restrictive because any of the modifications may achieve the desired result. Also, because these modifications are common techniques in the art, a worker of ordinary skill could readily modify a peptide of the invention using the above methods, without undue experimentation.

"The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 47 U.S.P.Q.2D 1705 (Fed. Cir. 1998). "The enablement requirement is met if the description enables any mode of making and using the invention." Johns Hopkins Univ., *supra*. (emphasis added).

The Examiner relies on the *Wands* test for enablement, and contends that a worker of skill in the art would have to undergo undue experimentation to practice the claimed invention. Applicants respectfully disagree. *Wands* involved screening of large numbers of hybridomas to identify specific hybridomas that fell within the claim limitations. The court in *Wands* indicates

that because Wands provided sufficient guidance to make and screen the hybridomas and presented working examples, that the enablement requirement was fulfilled. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). *In re Wands* does not hold that a specific number of working examples is required. In reaching a decision, the court in *Wands* considered that the inventor's disclosure provides considerable direction and guidance on how to practice the invention and presents working examples. *Id* at 740. This fact coupled with the high level of skill in the art renders the invention enabled in the courts' opinion. *Id.*

In the present application, the claims of the application are directed to a limited genus of peptides with specified amino acid length that bind to a specific cell receptor. The specification fully discloses methods to make the claimed peptides and methods to determine their binding specificity, and demonstrates binding to the receptor in the specification. Similar to *Wands*, the invention provides a composition that binds to a specific binding target with the binding identified using well-known screening methods. The present specification teaches methods to make the invention (e.g., peptide synthesis, phage display, other methods well-known in the art) and methods to screen the invention (e.g., VEGFR-3 binding assays), thereby providing ample guidance and direction to a worker of ordinary skill in the art. Also, the present specification provides several working examples, similar to the disclosure at issue in *Wands*. Moreover, the level of skill in the art of peptide synthesis and DNA manipulation is high.

Given the high level of skill in the art and the guidance provided by the Applicants to make and use peptides of the invention, a worker of ordinary skill would not be required to undertake undue experimentation to make or use the invention. The peptides of the invention require a specific sequence or limited variants within that sequence. Additionally, the peptide sequence is of a finite length, such that a limited number of peptides are available and the binding domain of the claimed peptide is short compared to other proteins or peptides. Therefore, making the peptide of the present invention and screening for activity are performed relatively quickly using routine techniques, and the total number of combinations is orders of magnitude smaller than where a large protein of complex structure is contemplated. The making and screening required by the present invention (peptide synthesis) involves more routine experimentation than that set forth in the facts of *In re Wands,* which the Court said was <u>not</u> undue experimentation. Experimentation, even if extensive, is not necessarily undue if it is routine in the art (*In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)).

Because Applicants have taught a worker of ordinary skill in the art to make and use the claimed peptides, with only routine screening experimentation, the rejection under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

VI. Claim 13 Is Allowable under 35 USC §112

While Applicants contend that, for the reasons stated herein, none of the pending claims should be rejected and are in condition for allowance, Applicants submit that the Examiner has, at the least, incorrectly maintained the rejection of claim 13 as lacking enablement under 35 USC §112, first paragraph.

Claim 13 is directed to an isolated peptide consisting of 8-100 amino acids comprising the sequence CGYWLTIWGC set out in SEQ ID NO: 35, which binds to VEGFR-3. In the final action, the Examiner acknowledges that Applicants have enabled a peptide of the CGYWLTIWGC sequence that binds to VEGFR-3, that inhibits VEGF-C/VEGFR-3 binding, a peptide dimer of the sequence, a pharmaceutical composition of the peptide, and several other aspects of the invention specifically related to the peptide (see page 6, paragraph 13 of the Final Action). Additionally, an amendment to claim 1 obviates the Examiner's objection to the term "comprising," because claim 13 depends from claim 1.

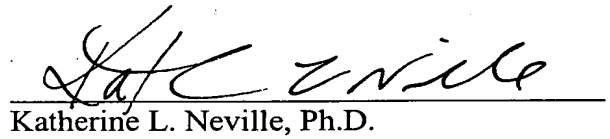
Because Applicants have clearly enabled a polypeptide "comprising" the specific sequence CGYWLTIWGC and demonstrated its claimed functionality in binding VEGFR-3, and because claim 13 is fully described in such a manner so that a person of ordinary skill in the art can make and use the invention, the rejection of claim 13 should be withdrawn.

VII. Conclusion

For the reasons given above, Applicants submit that the claims are in condition for allowance and request expedited notice of the same.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6357
(312) 474-6300

By: 

Katherine L. Neville, Ph.D.
Reg. No: 53,379
Agent for Applicants

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